12. (amended) A method for the treatment of hypercholesterolemia comprising administering to a mammal[, including man,] a therapeutically effective amount of a pharmaceutical composition for sustained release, comprising a water soluble salt of fluvastatin as active ingredient.

13. (amended) A method according to claim 12 wherein the [said] pharmaceutical composition is selected from the group [comprising] consisting of matrix formulations, diffusion-controlled membrane coated formulations[;] and combinations thereof.

Add the following new claim:

--14. The method according to claim 12 or 13, wherein the mammal is a human.--

REMARKS

Upon entry of the amendments herein, claims 1-8 and 12-14 are pending in the application. Claims 1, 2, 4, 6, 8, 12 and 13 have been amended; claims 9-11 have been canceled and new claim 14 has been added. No new matter has been introduced by any of the amendments herein.

Claims 1, 2, 5, 6 and 10-13 have been rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,462,749 to Rencher. The Examine asserts that "Rencher teaches a pharmaceutical delivery vehicle comprising xanthan gum ..." and that the reference further discloses 1) the use of water-insoluble

materials to retard release and 2) cholesterol-lowering agents as components of the formulations. The Examiner goes on to assert that it would have been obvious to combine the alleged teachings of Rencher with Applicants' acknowledgment that fluvastatin is known to reduce cholesterol levels to arrive at the instantly claimed pharmaceutical compositions. The Examiner is in error in this assessment.

The pharmaceutical carriers disclosed and claimed by Rencher are clearly designed to confer bioadhesive properties to the formulations for the purpose of topical treatment of mucous membranes or other moist areas of the human body. The Rencher blend of xanthan gum and sodium carboxymethylcellulose is chosen particularly for this purpose.

However, the present invention relates to the design of pharmaceutical compositions with sustained release of a water-soluble form of a particular drug, fluvastatin, which composition manifests a slow rate of release of the active ingredient with concomitant long duration of effect.

In those formulations according to the instant invention where xanthan gum is used, the aim is to provide a noneroding matrix formulation for sustained release; in such cases the xanthan gum is used alone, not in blend with sodium carboxy-methylcellulose or any other component. As clearly defined in the instant specification, the term "sustained release," a limiting term used in the instant claims is clearly defined as meaning release time of the drug of greater than three hours' and up to thirty hours' duration. On the other hand, in all the

Rencher examples the active ingredient is released within three hours. Thus, Rencher neither teaches nor suggests the sustained release formulations comprising fluvastatin salts according to the instant invention. Rencher teaches nothing to dispel the notion (see, particularly, page 9 of this response) that water-soluble salts of fluvastatin would be undesirable as active ingredients in the formulations of the instant invention. The rejection should be withdrawn.

Claims 1-4 and 9-13 have been rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,576,016 to Amselem, et al. or U.S. Patent No. 5,023,089 to Sakamoto, et al. The Examiner asserts that Amselem, et al. teach a vehicle comprising a lipid, particularly a wax, and that Sakamoto, et al. teach a vehicle comprising a fat, specifically paraffin. The Examiner further asserts that these teachings combined with Applicants' acknowledgment that fluvastatin is water-soluble render obvious the instant invention. The Examiner further argues that the instantly claimed erosion would be achieved due to the melting of the vehicle "over time in the manner of a suppository at body temperature." Further along these lines the Examiner refers to paraffin and the alleged teaching of Amselem, et al. that such would be a solid wax at 25°C. Even if all these assertions were correct, they would not be critical to the determination of patentability in this instance.

The formulation according to Amselem, et al. comprises a nanoemulsion of particles comprising a lipid core. In Amselem, et al., paraffin can be used to form particles from a mixture of

paraffin with other lipids to obtain a solid or liquid crystalline phase at 25°C or above; the mean diameter of the particles is 10 to 250 nm. However, paraffin in the instant formulations is used as the matrix form itself in a tablet formulation. According to the instant invention, paraffin is not mixed with other lipids to form emulsions. Contrary to the Examiner's contention, the tablets formulated according to the instant invention do not melt at body temperature; according to the USP/NF, the congealing range of paraffin is between 47° and 65°C, i.e., far higher than body temperature.

The Sakamoto, et al. preparations contain a mixed melt of two or more fats with different melting points, and the active ingredient is suspended or melted within said mixed melt. The suspension or melt is rendered into granular form or beads by spray cooling. On the other hand, according to the present invention, no melt of paraffin or mixed melt of fats is used to form the matrix tablet.

Claims 1, 2 and 7-13 have been rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,393,626 to Kotwal, et al. or U.S. Patent No. 5,238,686 to Eichel, et al. The Examiner asserts that both cited references teach coated vehicles for controlled release of water-soluble drugs and that in both references ethylcellulose may be used as the coating. The Examiner asserts that these alleged teachings in combination with Applicants' acknowledgment that fluvastatin is water-soluble render the instant invention obvious.

The problem addressed by Kotwal, et al. is the administration of highly water-soluble drugs in a controlled-released dosage form, but the solution to the problem is much different than that embodied in the present invention. The Kotwal, et al. formulation is a multi-layered, controlled-release pharmaceutical dosage form with as many as seven coating layers and which provides for constant release of highly water-soluble drugs over extended periods of time; this is a solution to the problem that reflects the understanding in the art and the assumption of the difficulty of achieving sustained release of a water-soluble active.

On the other hand, the solutions employed in the instant formulations comprise a coated, sustained-release formulation of water-soluble salts of fluvastatin; the high solubility of fluvastatin salts notwithstanding, sustained release can be achieved with only one coating layer by employment of the instant formulation technique.

The disclosure of Eichel, et al. relates to a dual-walled, coated, drug delivery system to provide sustained release of water-soluble drugs. This dual coating comprises an outer enteric coating and an inner controlled-release coating. Again, it is the Examiner's view that it would have been obvious to deliver fluvastatin in the vehicle of Eichel, et al. because of the knowledge that fluvastatin is water-soluble.

However, as was known in the art at the time of filing of the instant application, a substance with high solubility formulated in an insoluble porous membrane will be released at a

rate determined by the diffusion rate of the substance. The higher the solubility of the substance, the higher will be the concentration of the drug in the aqueous solution created by the penetrating gastrointestinal fluid; this will ultimately result in faster diffusional transport. A more rapid release of the drug could mean that the beneficial effects of sustained release administration are lost. Thus, according to the knowledge in the art, substances with high solubility, e.g., water-soluble salts of fluvastatin, would not be thought of as desirable active ingredients in the formulations disclosed in the present invention to obtain sustained release; in fact, one would, based on the knowledge in the art, tend to avoid substances such as the salts of fluvastatin in such a formulation.

Surprisingly, however, the instantly disclosed formulations do give favorable sustained release of water-soluble salts of fluvastatin. This is demonstrated in the examples set forth in the instant specification wherein the release of fluvastatin is compared to the release of two other water-soluble substances, methylparaben and diclofenac.

Examples 1 and 2 (results summarized in Figs. 1 and 2, respectively) show that the release of fluvastatin, both in eroding matrix and noneroding matrix sustained-release tablets, is slower than that of either methylparaben or diclofenac. These results were observed despite the higher aqueous solubility of fluvastatin.

Example 3 (results summarized in Fig. 3) provides further demonstration of the unexpectedly favorable extended release of

fluvastatin in matrix formulations. However, the results also indicate that this property is not attributable to every oral fluvastatin formulation; rather, it is limited to fluvastatin contained in certain types of sustained-release formulations employed in the practice of the instant invention.

In Example 4 (summarized in Fig. 4), the transport rates of diclofenac and fluvastatin across a membrane are compared for different initial concentrations of the drugs on the donor side in a two-compartment set-up. As anticipated, the diclofenac transport rate across the membrane increases on the donor side because of the increased driving force caused by the increased concentration. However, the transport rate of fluvastatin under these same conditions is, unexpectedly, essentially independent of the initial concentration. This experiment clearly shows the unexpected, particular superiority of fluvastatin for use in a formulation with a diffusion controlling membrane as disclosed in the present invention.

Applicants wish to remind the Examiner that the instant claims are limited to pharmaceutical compositions (and methods employing them) comprising a water-soluble salt of fluvastatin as active ingredient and that the instant invention is based on the discovery of properties of this active ingredient in water-soluble form that are unexpected in light of what has been observed for other water-soluble drugs.

Thus, the principle on which the present invention is based transcends the particulars of the references cited by the Examiner and the state of the art in general. None of the

references provide any hint of the unexpected benefits to be had from the present formulations, nor do any of them provide any motivation to try to make the present formulations in the face of expectations of ineffectiveness.

Claims 8 and 12 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The inadvertent misspelling of hydroxypropyl in claim 8 has been corrected. In claim 12, the phrase "including man" has been deleted; new, dependent claim 14, reciting the preferred embodiment of treating humans, has been added.

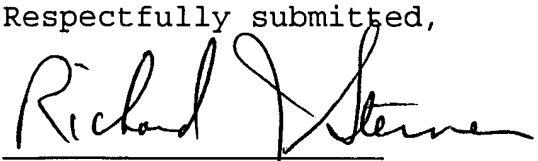
The claims have also been amended, where appropriate, to address certain other informalities, including nonconformance with 37 C.F.R. §1.75(c), and in the interest of enhancing the clarity of language. Similarly, the specification has been amended in a number of places to correct misspellings and informalities in language.

As set forth above, the instantly claimed subject matter is patentably distinct from the disclosure of the cited references. Furthermore, the amendments herein to the claims have put them into proper form for allowance. Reconsideration and allowance of pending claims 1-8 and 12-14 are respectfully requested.

The Assistant Commissioner is hereby authorized to charge any fee which may be due in connection with this communication to Deposit Account No. 23-1703.

Dated: November 17, 1999

Respectfully submitted,



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Enclosure